6.2 Platelet Differentiation

Six clinical studies (Studies 009, 015, 026, 032, 065 and 079) were undertaken to compare the effects of celecoxib with those of placebo and NSAIDs on platelet aggregation, thromboxane production, and bleeding times. A principal feature of these studies was that celecoxib was evaluated at doses exceeding the recommended clinical dose range for anti-inflammatory and analgesic efficacy. Celecoxib doses as high as 800 mg single dose and 1200 mg BID (for up to 10 days) were evaluated (Table 45).

Table 45. Summary of Celecoxib Platelet Differentiation Studies

Study No. - Population	Duration	No. of Subjects	Treatments
032 - Healthy adults	8 days	24	Celecoxib 600 mg BID, naproxen 500 mg BID, or placebo
065 - Healthy adults	8 days	51	Celecoxib 600 mg BID, diclofenac 75 mg BID, ibuprofen 800 mg TID, or placebo
079 - Healthy adults	10 days	56	Celecoxib 800 or 1200 BID, naproxen 500 mg BID, or placebo
009 - Healthy adults	single dose	37	Celecoxib 100, 400, or 800 mg, ibuprofen 800 mg; or placebo
026 - Healthy adults	6 days	6	Celecoxib 400 mg BID + aspirin 650 mg (single dose)
015 - Healthy adults	10 days	48	Celecoxib 200 mg BID or placebo

6.2.1 Placebo-Controlled Multiple-Dose Studies versus NSAIDs: Studies 032, 065 and 079

Three placebo-controlled multiple-dose studies comparing the platelet effects of supratherapeutic doses of celecoxib to therapeutic doses of NSAIDs were conducted. These studies were of similar design and examined the effects of celecoxib (600 mg, 800 mg or 1200 mg BID) on platelet aggregation induced by collagen and arachidonate, on bleeding time, and on serum thromboxane B_2 (TxB_2) levels.

In Study 032, healthy subjects received a single morning dose of celecoxib 600 mg (n=8), naproxen 500 mg (n=8), or placebo (n=8), followed 48 hours later by the same study medication administered BID for seven days and as a final morning dose on Day 10. Platelet aggregation, bleeding time, and serum TxB_2 were determined 30 minutes prior to and eight hours after the first dose of study medication on Day 1, and 30 minutes prior to and four, six, and eight hours after the final dose on Day 10.

In Study 065, healthy subjects received one of the following treatments for seven days and as a single dose on the morning of Day 8: celecoxib 600 mg BID (N=12), diclofenac 75 mg BID (N=12), ibuprofen 800 mg TID (N=13) or placebo (N=14). Platelet aggregation, bleeding time, and serum TxB_2 levels were determined 30 minutes prior to and 2, 4, and 6 hours after the morning dose on Day 1 and Day 8.

In Study 079, healthy subjects received a single morning dose of celecoxib 800 mg (n=12), naproxen 500 mg (n=8), or placebo (n=8) followed 48 hours later by the same study medication adminstered BID for ten days. A second group of healthy subjects (n=28) was studied in an identical fashion except that subjects randomized to celecoxib treatment received a single dose of 1200 mg followed 48 hours later by 1200 mg BID for 10 days. Platelet aggregation, bleeding time and serum TxB_2 concentrations were determined 15 minutes prior to and three and six hours following the administration of the initial (single dose; Day 1), the first BID dose following the 48 hour washout (Day 3), and the last BID dose (Day 12). In addition, these same determinations were performed two weeks after the end of dosing (Day 26).

6.2.1.1 Arachidonate-Induced Aggregation

The effects of celecoxib, placebo and NSAIDs on arachidonate-induced platelet aggregation are presented in Figure 25 and Table 46. In both studies, celecoxib 600 mg BID was indistinguishable from placebo in arachidonate-induced platelet aggregation at all time points. Naproxen had a statistically significant and sustained effect throughout the entire dosing period, including predose trough levels on Day 10. The effect of ibuprofen on Days 1 and 8 was similar to that of naproxen. The differences were significant versus placebo at all times measured. The effect of diclofenac was less extreme but still significant. Statistically significant differences versus placebo were present on Day 1 at two and four hours, and on Day 8 at six hours post-dosing.

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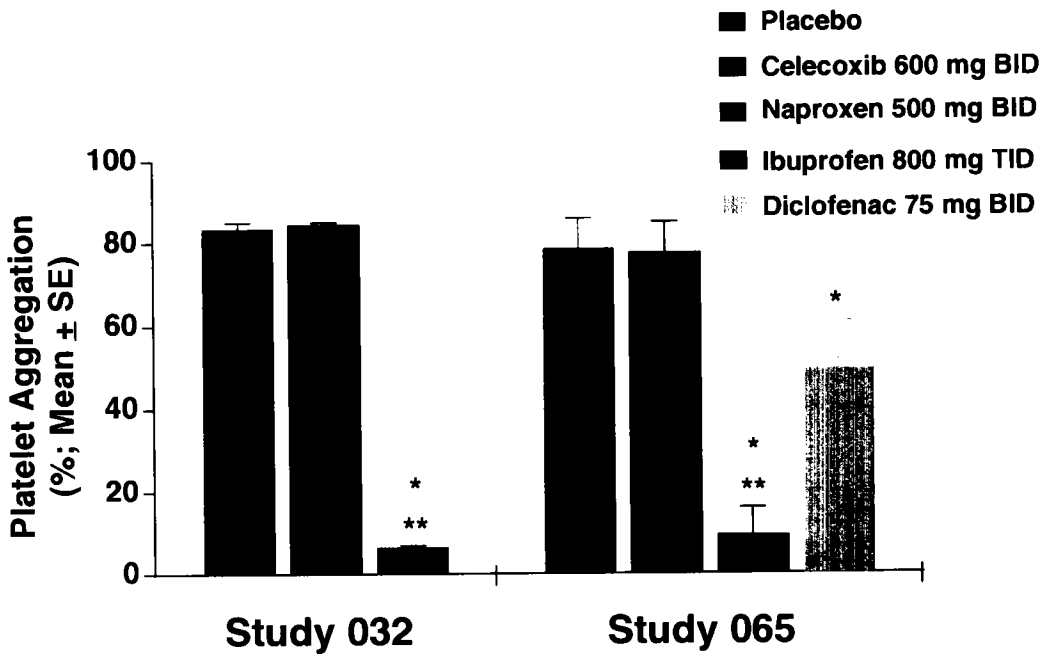
Figure 27. Platelet Aggregation to Arachidonate Following Multiple Doses: Studies 032 (Day 10, 8 hr) and 065 (Day 8, 6 hr)



* Significantly different from placebo; $p<0.05$.
** Significantly different from celecoxib; $p<0.05$.

Table 47 presents the effects of celecoxib 800 mg BID or 1200 mg BID, placebo and naproxen 500 mg BID on archidonate-induced platelet aggregation. Celecoxib 800 mg BID and 1200 mg BID did not significantly inhibit platelet aggregation. Celecoxib 800 mg BID was not statistically significantly different from placebo across the study. At two assessment times (Day 1, 3 hrs and Day 3, 6 hrs postdose) a statistically significant difference was detected between placebo and celecoxib 1200 mg BID; however, this difference was the result of decreased platelet aggregation in the placebo group and increased platelet aggregation in the celecoxib 1200 mg BID group. Naproxen produced a statistically significant and sustained reduction of arachidonate-induced platelet aggregation, including predose trough levels on Day 12, when compared to placebo.

Table 46. Arachidonate-Induced Platelet Aggregation (%): Studies 032 and 065

Study 032							
	Baseline(a)	Day 1	Day 10				
		8 hr	-30 min	4 hr	6 hr	8 hr	
Placebo (n=8)	82.6	85.5	87.0	84.3	83.9	82.8	
Celecoxib 600 mg BID (n=8)	86.9	86.1	85.7	85.3	87.5	84.4	
Naproxen 500 mg BID (n=8)	82.9	4.8*	4.8*	5.8*	5.1*	5.6*	
Study 065							
	Baseline(b)	Day 1			Day 8		
		2 hr	4 hr	6 hr	-30 min	2 hr	4 hr	6 hr
Placebo (n=14)	85.2	80.2	84.8	81.5	89.3	86.1	84.8	78.3
Celecoxib 600 mg BID (n=12)	85.2	75.1	76.3	83.8	85.0	86.8	78.3	76.7
Ibuprofen 800 mg TID (n=12)	85.8	8.7*	2.5*	31.2*	76.6*	14.8*	7.4*	9.1*
Diclofenac 75 mg BID (n=13)	85.5	36.4*	56.7*	71.3	84.0	79.3	55.2	49.3*

* Statistically significant difference ($p<0.05$) from placebo in change from Baseline.
a) Baseline Value is an average of Day 0 and Day 1 Predose measurements.
b) Baseline value is Day 1 Predose (-30 minutes).

Table 47. Arachidonate-Induced Platelet Aggregation (%): Study 079

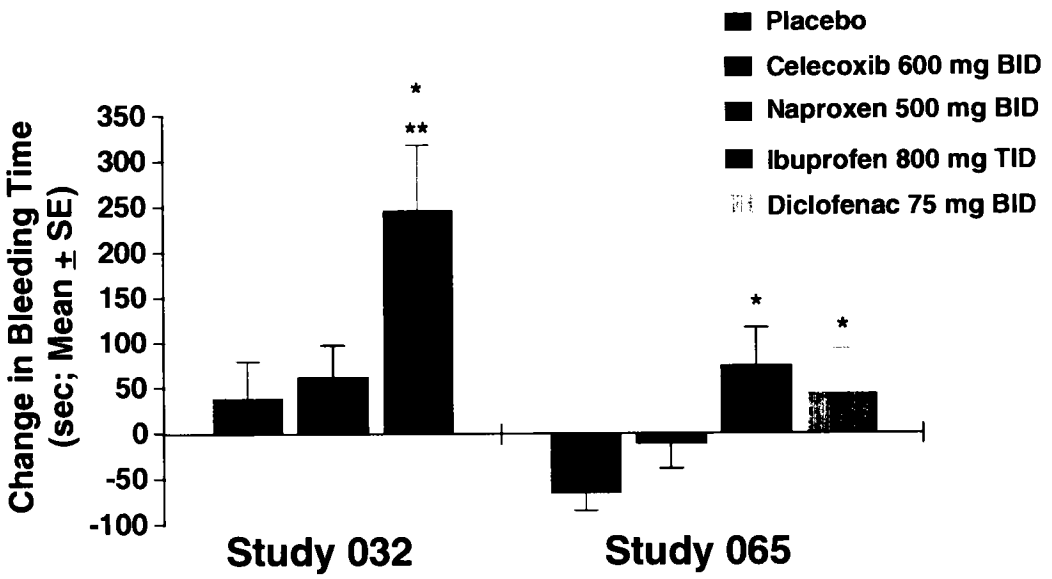
	Day 1			Day 3			Day 12			Day 26(b)
	Baseline(a)	3 hr	6 hr	-15 min	3 hr	6 hr	-15 min	3 hr	6 hr	
Placebo (n=16)	78.0	75.8	73.2	82.4	72.9	75.0	74.0	74.3	76.6	68.3
Celecoxib 800 mg BID (n=12)	73.6	68.2	61.2	69.3	67.4	74.0	74.7	77.6	70.1	70.2
Celecoxib 1200 mg BID (n=12)	70.8	80.6*	74.2	74.9	65.5	78.6*	68.4	67.4	65.5	72.7
Naproxen 500 mg BID (n=16)	73.4	2.6*	3.6*	75.8	4.2*	3.9*	3.4*	4.9*	4.6*	60.3

* Significantly different from placebo in change from Baseline; $p \leq 0.05$.
a) Baseline Value is Day 1 -15 min measurement.
b) Two weeks after last dose of study medication.

6.2.1.2 Bleeding Time

In both studies, celecoxib and placebo were not statistically different at any time during the study. In Study 032, naproxen caused a sustained significant increase versus placebo in bleeding time (Figure 28 and Table 48). In Study 065, diclofenac effects on bleeding time appeared to be reversible, with mean increases generally seen with the first post-Baseline dose which then returned toward Baseline, followed by an increase in bleeding time again after dosing on Day 8. The increases in bleeding time for diclofenac were significant compared to placebo on both Days 1 and 8. For ibuprofen an increase from the mean Baseline occurred after the first dose on Day 1 and was sustained on Day 8 without notable reversibility. Compared to placebo, both the Day 1 and Day 8 changes were significant.

Figure 28. Mean Changes from Baseline in Bleeding Time: Studies 032 (Day 10, 8 hr) and 065 (Day 8, 6 hr)



* Significantly different from placebo; $p<0.05$
** Significantly different from celecoxib; $p<0.05$

Table 48. Mean Changes from Baseline in Bleeding Time (Seconds): Studies 032 and 065

Study 032							
	Baseline(a) Mean Value	Mean Change from Baseline					
		Day 1			Day 10		
		8 hr			-30 min	4 hr	6 hr	8 hr
Placebo (n=8)	290.3	114.0			45.5	33.3	76.5	38.1
Celecoxib 600 mg BID (n=8)	264.0	100.8			44.6	91.9	53.0	60.5
Naproxen 500 mg BID (n=8)	265.4	246.9			178.9*	271.8	299.2*	244.7*
Study 065								
	Baseline(b) Mean Value	Mean Change from Baseline						
		Day 1			Day 8			
		2 hr	4 hr	6 hr	-30 min	2 hr	4 hr	6 hr
Placebo (n=14)	313.9	-53.6	-53.0	-50.2	-64.8	-32.8	-40.4	-63.0
Celecoxib 600 mg BID (n=12)	314.4	-31.8	-48.7	-51.3	63.8	0.2	5.7	-9.3
Ibuprofen 800 mg TID (n=12)	305.8	80.8*	68.1*	12.2	52.6*	50.6*	133.8*	72.5*
Diclofenac 75 mg BID (n=13)	325.1	116.8	20.6*	-24.4	-50.0	-35.1	78.1	43.0*

* Significantly different from placebo; $p \leq 0.05$.
a) Baseline Value is an average of Day 0 and Day 1 Predose measurements.
b) Baseline value is Day 1 Predose (-30 minutes).

In Study 079 bleeding times with celecoxib 1200 mg BID were not significantly different from placebo at any time during the study and celecoxib 800 mg BID was associated with significantly greater bleeding time only at the Day 12 post-dose assessments

(Table 49). In contrast, naproxen produced a sustained statistically significant increase in bleeding time versus placebo following dosing on Day 3 and Day 12.

Table 49. Mean Changes from Baseline in Bleeding Time (Seconds): Study 079

	Day 1			Day 3			Day 12			Day 26(b)
	Baseline(a) (Mean)	3 hr	6 hr	-15 min	3 hr	6 hr	-15 min	3 hr	6 hr	
Placebo (n=16)	289.4	24.9	59.1	43.7	21.1	54.4	29.0	23.6	-12.6	55.3
Celecoxib 800 mg BID (n=12)	283.3	85.6	55.0	113.7	119.9	54.9	28.7	197.5*	135.7*	55.6
Celecoxib 1200 mg BID (n=12)	300.2	2.5	8.1	124.5	78.7	126.1	38.7	37.6	73.2	34.3
Naproxen 500 mg BID (n=16)	327.9	140.7	235.3	75.0	226.9*	244.3*	159.3	250.9*	188.4*	121.9

* Significantly different from placebo in change from Baseline; p≤0.05.
a) Baseline Value is Day 1 -15 min measurement.
b) Two weeks after last dose os study medication.

6.2.1.3 Serum TxB_2 Levels

Figure 29 shows the results of serum TxB_2 assays. For naproxen and ibuprofen, the mean decrease in serum TxB_2 levels exceeded 200 ng/mL at all post-Baseline measurements. Decreases for diclofenac were not as great as with naproxen but compared to placebo, diclofenac significantly reduced TxB_2 levels on both Day 1 and Day 8. Table 50 shows the statistical comparisons of the mean changes.

Celecoxib was associated with some decreases in serum TxB_2 levels but less than those seen with naproxen, ibuprofen and diclofenac. In Study 032, celecoxib was associated with minor decreases in serum TxB_2 levels, although none of the changes were significant versus placebo. In Study 065, celecoxib treatment was associated with decreases of approximately 85 ng/mL on Day 1, and slightly larger decreases on Day 8. This compares to a maximal placebo decrease of approximately 30 ng/mL in this study. The differences versus placebo were statistically significant at some time points.

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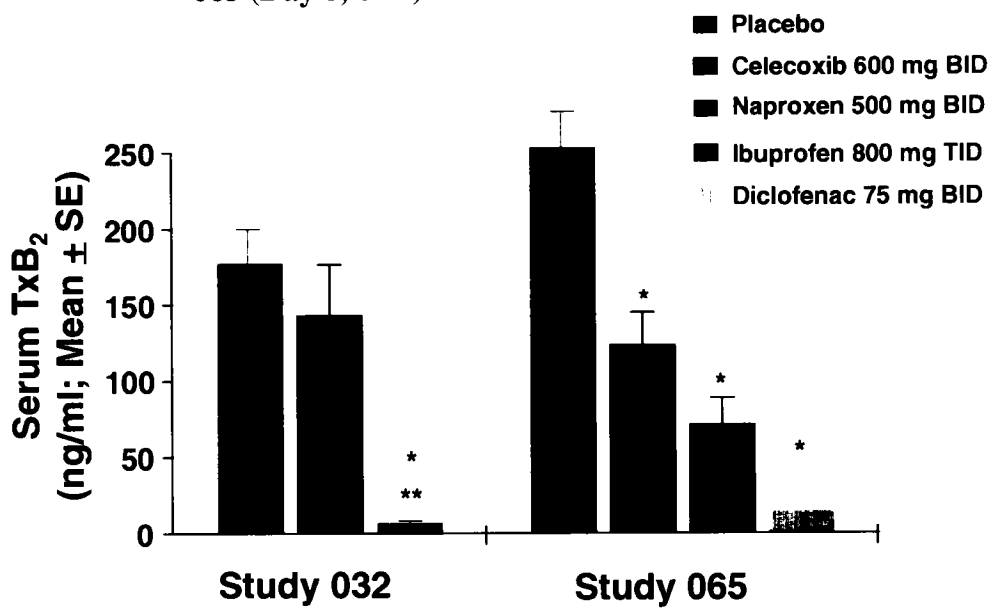
Figure 29. Mean Serum TxB_2 Levels: Studies 032 (Day 10, 8 hr) and 065 (Day 8, 6 hr)



* Significantly different from placebo; $p<0.05$
** Significantly different from celecoxib; $p<0.05$

Table 50. Mean Serum TxB_2 Levels (ng/mL): Studies 032 and 065

	Study 032						
	Baseline(a)	Day 1			Day 10		
		8 hr			-30 min	4 hr	6 hr	8 hr
Placebo (n=8)	179.0	200.3			160.0	160.4	132.5	170.5
Celecoxib 600 mg BID (n=8)	180.9	148.2			101.7	88.4	99.8	138.1
Naproxen 500 mg BID (n=8)	220.2	9.3*			8.0*	2.3*	2.8*	4.5*
	Study 065							
	Baseline(a)	Day 1			Day 8			
		2 hr	4 hr	6 hr	-30 min	2 hr	4 hr	6 hr
Placebo (n=14)	237.4	245.3	220.5	259.4	231.8	218.3	260.3	250.3
Celecoxib 600 mg BID (n=12)	257.4	163.5*	178.8	176.6*	166.6	130.7	121.6*	128.0*
Diclofenac 75 mg BID (n=12)	251.3	87.0*	112.0*	130.2*	158.9	157.3	98.4*	75.4*
Ibuprofen 800 mg TID (n=13)	215.3	3.6*	6.6*	15.6*	64.5*	10.7*	8.1*	12.3*

* Significantly different from placebo in change from Baseline; $p\leq0.05$.
a) Baseline value is Day 1 Predose (-30 minutes).

The effect of treatment on serum TxB_2 levels in Study 079 are reported in Table 51. For naproxen 500 mg BID, serum TxB_2 levels decreased significantly when compared to placebo, similar to the findings observed in Study 032. The mean changes in serum TxB_2 levels with celecoxib 1200 mg BID were also statistically significantly reduced when compared to placebo at most assessments. The mean changes with celecoxib 800 mg BID were significantly different from placebo at fewer assessments. The mean

changes in serum TxB_2 levels with celecoxib 800 mg BID and 1200 mg BID in Study 079 were similar in magnitude to the changes seen with celecoxib 600 mg BID in Studies 032 and 065.

Table 51. Mean Serum TxB_2 Levels (ng/mL): Study 079

	Day 1			Day 3			Day 12			Day 26(b)
	Baseline(a)	3 hr	6 hr	-15 min	3 hr	6 hr	-15 min	3 hr	6 hr	
Placebo (n=16)	221.8	210.1	229.0	210.8	229.6	185.7	233.3	254.1	243.1	150.0
Celecoxib 800 mg BID (n=12)	187.9	125.7	134.9*	165.9	131.5*	131.1	143.2	142.2*	140.1*	148.2
Celecoxib 1200 mg BID (n=12)	221.5	152.3	122.5*	190.7*	121.4*	127.6*	123.0*	105.1*	112.1*	155.7
Naproxen 500 mg BID (n=16)	205.0	8.8*	6.9*	75.1*	5.8*	5.8*	7.6*	3.4*	26.3*	131.6

* Significantly different from placebo in change from Baseline; p≤0.05.
a) Baseline Value is Day 1 -15 min measurement .
b) Two weeks after last dose of study medication.

6.2.2 Single Dose Platelet Study: Study 009

In this double-blind study healthy subjects received a single dose of either celecoxib 100 mg, celecoxib 400 mg, celecoxib 800 mg, ibuprofen 800 mg or placebo. The effects of celecoxib 100, 400, and 800 mg on platelet aggregation induced by arachidonate were statistically indistinguishable from that of placebo (Table 52). In contrast, ibuprofen was associated with statistically significant inhibition of arachidonate-induced aggregation at three hours postdose.

Table 52. Mean Changes (± SE) from Baseline in Platelet Aggregation: Study 009

Agonist	Placebo (n=7)	Celecoxib 100 mg (n=7)	Celecoxib 400 mg (n=7)	Celecoxib 800 mg (n=7)	Ibuprofen 800 mg (n=7)
Arachidonate-induced aggregation					
3 hr postdose	1.3 ± 3.7	-2.1 ± 2.5	-10.1 ± 9.0	-9.1 ± 13.7	-66.6 ± 11.6*
8 hr postdose	-1.7 ± 5.4	-0.6 ± 5.9	-2.9 ± 3.7	-15.0 ± 12.0	-33.0 ± 14.7
24 hr postdose	5.6 ± 3.5	-0.6 ± 4.9	4.3 ± 4.6	-12.6 ± 12.0	-3.1 ± 3.4

* Significantly different from placebo; p<0.05.

Effects on bleeding time were highly variable; no significant effect was seen in any of the treatment groups. Serum TxB_2 levels were reduced 3-4 fold more in the ibuprofen group compared to celecoxib and placebo groups, and the difference from placebo was statistically significant at all time points. Celecoxib had no significant effects on serum TxB_2 levels when compared to placebo.

6.2.3 Open-Label Platelet Function Study: Study 026

Study 026 was an open-label, multiple-dose study of the effects of celecoxib on platelet function in six healthy male subjects who received celecoxib 400 mg BID for six days. After a seven-day washout period, all subjects had platelet aggregation and whole blood TxB_2 levels determined after receiving a single dose of aspirin 650 mg. The differences between celecoxib and aspirin were statistically significant at both two and four hours after dosing for changes from pretreatment in aggregation response to arachidonate (Table 53) and for TxB_2 levels. These study results provide additional data to indicate that celecoxib does not affect platelet function, and is significantly different from a nonselective COX-1 and COX-2 inhibitor, in this case aspirin.

Table 53. Mean Changes (± SE) from Baseline in Platelet Aggregation: Study 026

	Celecoxib 400 mg BID	Aspirin 650 mg SD
Arachidonate-induced aggregation, % change		
2 hr postdose	-0.5 ± 3.3 *	-44.2 ± 9.8
4 hr postdose	-0.5 ± 4.6 *	-39.7 ± 9.6

* Significantly different from aspirin; $p<0.05$.

6.2.4 Platelet Effects in Healthy Elderly Subjects: Study 015

Study 015 was a 14-day, randomized, double-blind, placebo-controlled study which compared the pharmacokinetic and pharmacodynamic profiles of celecoxib in 24 healthy elderly subjects to 24 non-elderly subjects. The placebo group consisted of four healthy elderly and four healthy non-elderly subjects. As part of this study, platelet aggregation responses to collagen and arachidonate were measured before dosing and at three and eight hours after dosing on Days 1 and 9. There were no statistically significant differences between the young and the elderly celecoxib-treated patients in platelet aggregation to collagen or arachidonate.

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6.2.5 Conclusions

The results of replicate platelet function studies demonstrated that:

- Celecoxib did not affect platelet aggregation and bleeding times, even when given at doses up to 12-fold higher than the maximum recommended therapeutic dose.
- Supratherapeutic doses of celecoxib may result in reductions of serum TxB_2 levels, which are insufficient to affect bleeding time or platelet aggregation.
- NSAIDs at therapeutic doses were shown to reduce significantly both serum TxB_2 levels and platelet function.

6.3 General Safety Profile

6.3.1 Extent of Exposure

A total of 13,072 unique individuals have received at least one dose of study medication in the celecoxib clinical trials. Table 54 summarizes the numbers of patients exposed to celecoxib, placebo, NSAIDs or other drugs, and combinations of celecoxib and other drugs.

Table 54. Summary of Unique Treated Subjects/Patients: Combined Studies

Treatment/Dose Level	No. of Unique Subjects/Patients Treated
Placebo	1354
Celecoxib	
5-1200 mg single dose	780
5-50 mg BID	948
100 mg BID	3261
200 mg QD	500
200 mg BID	3272
400 mg BID	665
600-1200 mg BID	20
Any Dose	9463
Celecoxib + Other Drug	17
NSAID Control or Other Drug	2255

5-50 mg = 5, 20, 25, 40, or 50 mg
600-1200 mg = 600, 800, 900, or 1200 mg
Unique = each individual is counted only once. Subjects/patients who participated in multiple periods of a crossover study or were treated in more than one study are only counted once. If a subject/patient received both placebo or a comparator and celecoxib, he/she is counted only as a celecoxib subject/patient.

The studies of greatest interest with respect to duration of exposure are the arthritis studies, since they represent all cases of chronic celecoxib administration. The intervals of exposure in these studies are summarized in Table 55. A total of 8,139 patients have received at least one dose of celecoxib in a controlled arthritis study or the North American Long-term, Open-label Arthritis Study.

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Table 55. Duration of Exposure to Any Dose of Celecoxib: Controlled Arthritis Studies and North American Long-Term Open-Label Arthritis Study Combined

Time of Exposure	Cumulative No. of Patients (Any Dose and Regimen)
≥ 1 day	8139
≥ 2 weeks	7599
≥ 6 weeks	6123
≥ 13 weeks	3859
≥ 26 weeks	2429
≥ 39 weeks	1598
≥ 52 weeks	981
≥ 64 weeks	312

Table 56 summarizes the extent of exposure in the arthritis trials by patient-years of treatment at the various dose levels. Celecoxib has been administered for a total of over 3200 patient years at all doses combined. The majority of exposure to celecoxib in arthritis studies (over 2200 patient-years) has been at doses of 100 and 200 mg BID or 200 mg QD, the recommended doses for treating arthritis and pain.

Table 56. Patient-Years of Exposure to Celecoxib: All Arthritis Studies

Study Type	50 mg BID	100 mg BID	200 mg BID	200 mg QD	400 mg BID	Any Dose
Controlled arthritis	116.1	289.3	465.7	47.1	87.1	1020.3
Total (Including long-term open-label)	116.6	679.9	1567.0	47.1	499.4	3267.5

Frequently reported adverse events and withdrawals due to adverse events are presented for three distinct groups; the North American Controlled Arthritis Trials, the International Arthritis Trials and the North American Long-term Open Label Arthritis Study.

6.3.2 North American Controlled Arthritis Trials

The North American Controlled Arthritis Trials are a group of controlled studies performed in patients with OA and/or RA, in which patients were treated for two to 12 weeks with celecoxib (50-800 mg/day; BID or QD dosing), placebo, or an NSAID (naproxen, ibuprofen, or diclofenac).

In the North American Controlled Arthritis Trials, there were 9,666 treated patients: 5,704 celecoxib, 1,864 placebo, and 2,098 NSAIDs. In this patient population, the

overall mean age for patients receiving celecoxib was 59.5 years, compared with 60.0 years in placebo patients and 58.8 years in patients receiving NSAID control (naproxen, diclofenac, or ibuprofen). In all treatment groups, female patients predominated, with the proportion ranging from 66.2% to 72.7%. The patients in these studies were predominantly Caucasian (>82% in all treatment groups), followed by Black and then Hispanic patients. For female patients, mean weights across treatment groups ranged from 76.7 to 88.6 kg. Mean weights of male patients ranged from 88.0 to 97.0 kg.

6.3.3 International Arthritis Trials

Studies 042 and 041 were 6-week OA and 24-week RA efficacy studies, respectively, that were conducted at sites in Australia, Europe, Isreal, New Zealand, and South Africa. Patients with symptomatic arthritis were eligible for the studies, but a symptomatic flare was not required for enrollment.

A total of 1,342 arthritis patients were enrolled in the International Arthritis Trials. All patients receiving celecoxib 100 mg BID (n=346) or diclofenac 50 mg BID (n=341) were enrolled in the six-week OA efficacy study (Study 042), while all patients receiving celecoxib 200 mg BID (n=326) or diclofenac SR 75 mg BID (n=329) were enrolled in the 24-week RA efficacy study (Study 041). In the celecoxib groups, the mean ages were 63.3 years for 100 mg BID and 55.9 years for 200 mg BID, compared to 64.1 and 54.5 years for diclofenac patients receiving 50 and 75 mg BID, respectively). The gender distribution was similar to that in the North American Arthritis Trials, with the proportion of female patients ranging from 71.1% to 75.8%. The patients in these studies were predominantly Caucasian. The mean weights for female patients were 76.2 kg for celecoxib 100 mg BID, 78.0 kg for diclofenac 50 mg BID, 67.1 kg for celecoxib 200 mg BID, and 66.3 kg for diclofenac SR 75 mg BID. For male patients, mean weights were 86.9 kg for celecoxib 100 mg BID, 85.2 kg for diclofenac 50 mg BID, 81.2 kg for celecoxib 200 mg BID, and 80.6 kg for diclofenac SR 75 mg BID.

6.3.4 North American Long-term Open-Label Arthritis Study: Study 024

The principal objective of Study 024 is to evaluate the safety of administering celecoxib for up to two years in patients with OA or RA. Patients were eligible to enter the open-label trial upon completing participation in one of nine controlled arthritis trials. All OA patients who entered the trial started with a 100 mg BID dose of celecoxib and had the

option to escalate their dose to 200 mg BID. All RA patients who entered the study started with a celecoxib dose of 200 mg BID and had the option to increase this dose to 300 mg BID or 400 mg BID. A total of 4499 patients (2554 OA patients and 1945 RA patients) have been enrolled. This study is ongoing. Table 57 summarizes the enrollment status as a function of the dose and duration for the study.

Table 57. Numbers of Patients at Various Exposures: North American Long-term Open Label Arthritis Study

	50 mg BID	100 mg BID	200 mg BID	300 mg BID	400 mg BID	Any Dose
> 3 mo.	7	637	1748	423	656	3517
> 6 mo.	0	236	941	222	410	2363
> 9 mo.	0	151	548	104	211	1573
> 12 mo.	0	62	234	30	56	965

Data from 4499 OA and RA patients enrolled into Study 024. Patients are counted once per dose column but may appear in several columns due to dose adjustment.

6.3.5 Frequently Reported Adverse Events

6.3.5.1 North American Controlled Arthritis Trials

Table 58 shows the most common events in any treatment group (excluding celecoxib 25 to 40 mg BID), sorted by descending incidence in the celecoxib 200 mg BID column for the North American Controlled Arthritis Trials. A total of 12 types of adverse event occurred in at least 3% of the patients in any treatment group. Six of the 12 types of adverse event were GI in nature and with the exception of diarrhea, GI adverse events were more common in patients receiving NSAIDs than in celecoxib patients. Headache was the most common adverse event, with the highest incidence among placebo patients. In general, the varying adverse event incidences among the celecoxib groups do not suggest a dose-response effect. (Note that the celecoxib 200 mg QD group includes only patients from six-week studies. All other columns include patients from at least two 12-week studies.)

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Table 58. Adverse Events with Incidence ≥3% in Any Treatment Group: North American Controlled Arthritis Trials

		Celecoxib					
Adverse Event	**Placebo**	**50 mg BID**	**100 mg BID**	**200 mg QD**	**200 mg BID**	**400 mg BID**	**NSAID**
No. treated	1864	690	1779	453	1914	615	2098
Any event	54.6	63.6	60.2	51.9	62.5	60.2	66.7
Headache	20.2	16.7	17.0	17.7	14.3	14.5	14.8
Dyspepsia	6.2	8.1	8.7	4.6	9.9	8.1	12.0
URTI	6.7	9.0	8.1	5.3	8.8	7.0	9.9
Diarrhea	3.8	5.4	5.0	3.5	6.6	6.5	6.1
Sinusitis	4.3	5.2	4.9	3.1	5.5	5.4	4.6
Abdominal pain	2.8	4.5	3.4	2.0	5.2	3.3	8.2
Nausea	4.2	3.8	3.6	2.4	3.7	3.6	5.6
Back pain	3.6	1.7	2.9	2.2	3.0	0.8	2.0
Accidental injury	2.3	2.6	3.0	2.4	2.9	2.4	2.9
Rash	2.1	2.5	2.2	1.1	2.5	3.4	1.8
Flatulence	1.0	2.3	2.1	2.2	2.3	2.0	3.7
Constipation	1.9	1.4	1.8	1.1	1.9	0.8	4.1

All numbers are percentages of patients unless otherwise specified.

Table 59 shows statistical analyses of adverse events among treatment groups. For the purpose of all such analyses, the celecoxib column includes all patients receiving full therapeutic doses of celecoxib (100 mg BID, 200 mg QD, or 200 mg BID). Further, when celecoxib is being compared with placebo, only patients in placebo-controlled studies are included in the celecoxib group; similarly, in comparisons of celecoxib incidences with those of NSAIDs, only patients from active-controlled studies are included in the celecoxib column. This accounts for the different numbers of patients between the two celecoxib columns in the analysis tables.

A statistically significant difference ($p \leq 0.05$) was found between celecoxib (all 100 mg and 200 mg doses combined) and either placebo or NSAIDs for nine of the 12 adverse events that occurred with an incidence ≥3% (Table 59). The incidence of dyspepsia, abdominal pain, nausea, flatulence and constipation were significantly greater in patients receiving NSAIDs than those who were treated with celecoxib. Dyspepsia, upper respiratory tract infection (URTI), diarrhea, and flatulence were significantly higher in celecoxib-treated patients when compared to those receiving placebo.

Table 59. Analysis of Adverse Events between Celecoxib 100 mg BID, 200 mg QD and 200 mg BID and Placebo or NSAIDs

Adverse Event	Celecoxib*	Placebo	p Value	Celecoxib*	NSAID	p Value
No. treated	3512	1864	-	2890	2098	-
Any event	59.9	54.6	<0.001	63.9	66.7	0.044
Headache	16.8	20.2	0.002	16.0	14.8	-
Dyspepsia	8.4	6.2	0.004	9.9	12.0	0.021
URTI	8.4	6.7	0.029	9.4	9.9	-
Diarrhea	5.4	3.8	0.008	6.2	6.1	-
Sinusitis	4.8	4.3	-	5.6	4.6	-
Abdominal pain	3.5	2.8	-	4.9	8.2	<0.001
Nausea	3.6	4.2	-	3.8	5.6	0.002
Back pain	2.7	3.6	-	3.0	2.0	0.038
Accidental injury	2.8	2.3	-	3.1	3.0	-
Rash	2.4	2.1	-	2.6	1.8	-
Flatulence	2.1	1.0	0.003	2.2	3.7	0.003
Constipation	1.8	1.9	-	1.9	4.1	<0.001

Data are expressed in percentages of patients (except for p values).
*Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

Table 60 shows an analysis similar to that above except that celecoxib 400 mg BID is compared with placebo and NSAIDs, since it represents the highest celecoxib dose studied in North American Controlled Arthritis Trials and twice the highest recommended dosage. Significantly higher incidences of dyspepsia and diarrhea for celecoxib 400 mg BID compared to placebo were observed. Constipation was significantly more common for NSAIDs than for celecoxib.

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Table 60. Analysis of Adverse Events between Celecoxib 400 mg BID and Placebo or NSAIDs

Adverse Event	Celecoxib 400 mg BID	Placebo	p Value	Celecoxib 400 mg BID	NSAID	p Value
No. treated	615	636	-	434	443	-
Any event	60.2	55.3	-	62.0	63.0	-
Headache	14.5	22.0	<0.001	15.2	14.0	-
Dyspepsia	8.1	4.9	0.021	8.8	12.4	-
URTI	7.0	7.7	-	8.3	12.2	-
Diarrhea	6.5	3.5	0.013	6.5	4.1	-
Sinusitis	5.4	4.9	-	4.8	3.8	-
Abdominal pain	3.3	2.7	-	3.5	5.9	-
Nausea	3.6	4.6	-	4.1	4.1	-
Back pain	0.8	3.6	<0.001	0.9	0.9	-
Accidental injury	2.4	2.4	-	3.0	1.8	-
Rash	3.4	2.0	-	3.2	1.8	-
Flatulence	2.0	0.8	-	1.8	1.8	-
Constipation	0.8	2.7	0.016	0.7	2.9	0.020

Data are expressed in percentages of patients (except for p values).

6.3.5.2 North American Controlled Arthritis Trials: OA and RA Populations

Two differences in patient characteristics between the OA and RA populations from the North American Controlled Arthritis Trials were evident when demographic data were compared. In general, mean ages in patients with OA were approximately seven years higher than in RA patients. Further, for both sexes, mean weights were approximately 10 kg higher for OA patients than for RA patients.

Table 61 separately lists adverse event incidences for OA and RA patients from the North American Controlled Arthritis Trials. Comparison of the adverse events between OA and RA patients demonstrates no clinically important differences between the populations, despite the differences in mean age, the systemic nature of RA, and the increased use of concomitant medications to treat RA compared with OA.

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Table 61. Comparison of Adverse Events between OA and RA Patients: North American Controlled Arthritis Trials

	OA				RA			
Adverse Event	**Placebo**	**100 mg BID**	**200 mg BID**	**NSAID**	**Placebo**	**100 mg BID**	**200 mg BID**	**NSAID**
No. treated	1329	1311	1208	1388	535	468	706	710
Any event	54.3	59.3	63.8	68.1	55.5	62.6	60.3	63.9
Headache	19.3	17.1	14.1	14.7	22.6	16.7	14.6	15.1
Dyspepsia	6.5	8.2	10.7	12.0	5.6	10.0	8.5	12.1
URTI	6.3	7.2	8.6	9.4	7.7	10.5	9.1	10.8
Diarrhea	3.8	4.8	7.2	7.1	3.7	5.6	5.5	4.2
Abdominal pain	2.8	3.1	6.2	9.1	3.0	4.1	3.4	6.3
Sinusitis	4.1	4.7	5.0	4.3	4.7	5.8	6.2	5.1
Nausea	3.8	3.5	4.0	6.6	5.4	3.8	3.3	3.7
Back pain	3.6	3.0	3.6	2.7	3.6	2.6	1.8	0.8
Accidental injury	2.2	3.5	3.1	3.5	2.4	1.7	2.4	1.7
Peripheral edema	1.3	1.6	3.0	2.4	0.7	1.3	1.8	1.5
Insomnia	2.7	2.6	2.6	2.2	1.3	1.9	2.3	2.5
Flatulence	1.1	1.9	2.3	4.3	0.7	2.8	2.3	2.5
Constipation	1.5	1.9	2.2	4.9	2.8	1.5	1.4	2.4
Pharyngitis	1.1	2.2	2.2	1.9	0.9	2.6	3.0	1.5
Coughing	1.1	1.6	1.6	2.4	1.5	1.9	3.1	1.7
Rash	2.0	2.0	1.5	1.8	2.2	3.0	4.1	1.8

Includes any adverse event with incidence ≥3% in either the celecoxib 100 mg BID or 200 mg BID group or a control group in either OA or RA.

6.3.5.3 International Arthritis Trials

Table 62 shows the most common events in any treatment group in the International Arthritis Studies. A total of 19 types of adverse event occurred in at least 3% of patients in any treatment group. Unlike the North American Controlled Arthritis Trials, in which headache was consistently the most common event, diarrhea was the most common event in the 6-week OA study, and diarrhea, dyspepsia, and abdominal pain were more common than headache in the 24-week RA study. For all adverse events in Table 62, the incidence was higher for celecoxib 200 mg BID than for celecoxib 100 mg BID. This difference likely results from the longer duration of the RA trial (24 weeks compared with six weeks for OA).

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Table 62. Adverse Events with Incidence ≥3% in Any Treatment Group: International Arthritis Trials

Adverse Event	6 Week OA (Study 042)		24 Week RA (Study 041)	
	Celecoxib 100 mg BID	Diclofenac 50 mg BID	Celecoxib 200 mg BID	Diclofenac SR 75 mg BID
No. treated	346	341	326	329
Any event	43.6	52.8	68.1	72.6
Diarrhea	6.4	7.6	12.0	14.0
Abdominal pain	4.9	6.7	11.0	20.7
Dyspepsia	3.2	6.7	9.8	12.8
Headache	4.3	7.3	9.2	5.8
URTI	2.0	2.3	5.8	9.1
Nausea	3.2	5.0	4.6	8.2
Back pain	1.7	0.3	4.3	2.1
Dizziness	1.7	2.1	3.7	4.0
Edema peripheral	2.0	2.3	3.4	1.5
Fatigue	1.2	0.9	3.4	4.9
Pharyngitis	0.9	0.3	3.4	2.7
Coughing	0.9	0.0	3.1	2.4
Influenza-like symptoms	1.7	1.8	3.1	4.0
Rash	2.3	0.3	2.5	4.0
Pruritus	1.7	2.1	2.1	3.6
Flatulence	1.4	1.5	2.1	4.3
Vomiting	1.2	0.9	1.8	5.2
Anemia	0.0	0.3	1.5	3.0
Stomatitis	0.3	0.6	0.9	3.6

All numbers are percentages of patients unless otherwise specified.

6.3.5.4 North American Long-term Open Label Arthritis Study

Adverse events occurring at an incidence of 3% or greater in the long-term open label arthritis study (Study 024) are shown in Table 63. These adverse events generally occurred at an incidence greater than that observed with the 200 mg BID dose of celecoxib in the North American Controlled Arthritis Trials (Table 58). However, when normalized for time of exposure, the incidence for all of the adverse events listed in Table 59, except for bronchitis, are lower in Study 024 when compared to celecoxib 200 mg BID in the North American Arthritis Trials. These data provide no evidence to suggest that there is an increasing incidence for frequently occurring adverse events (≥ 3%) with increasing duration of exposure to celecoxib.

Table 63. Adverse Events with ≥3% Incidence: North American Long-term Open Label Arthritis Trial

	Long-term Open Label Arthritis Study (n=4499)		North American Controlled Arthritis Trials* (n=1914)	
Adverse Event	Incidence (% of Patients)	Events Per 100 Patient-Years	Incidence (% of Patients)	Events Per 100 Patient-Years
Headache	16.0	26.9	14.3	58.6
URTI	14.1	23.8	8.8	36.1
Dyspepsia	10.1	17.0	9.9	40.6
Sinusitis	9.2	15.6	5.5	22.5
Diarrhea	7.7	13.0	6.6	27.1
Accidental injury	7.2	12.0	2.9	11.8
Abdominal pain	5.5	9.3	5.2	21.3
Nausea	5.4	9.0	3.7	15.2
Back pain	4.3	7.2	3.0	12.2
Rash	4.2	7.1	2.5	10.1
Bronchitis	4.2	7.0	1.0	4.1
Dizziness	4.1	6.9	2.1	8.8
Peripheral edema	3.8	6.4	2.6	10.5
Coughing	3.5	5.9	2.1	8.8
Insomnia	3.4	5.7	2.5	10.1
Rhinitis	3.1	5.3	1.9	7.9
Urinary tract infection	3.2	5.3	1.2	4.9

* This column shows the incidence of adverse events for the celecoxib 200 mg BID dose group.

6.3.6 Adverse Events Leading to Withdrawal

6.3.6.1 North American Controlled Arthritis Trials

Table 64 shows the most common adverse events leading to discontinuation of study treatment. Overall, the incidences of any adverse event causing withdrawal ranged from 3.3% to 7.8% in patients receiving celecoxib, and no dose response relationship was evident. The highest incidence occurred in patients receiving an NSAID (9.7%). Seven types of adverse event led to withdrawal in at least 0.5% of patients in any treatment group.

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Table 64. Adverse Events Causing Withdrawal with an Incidence ≥0.5% in Any Treatment Group: North American Controlled Arthritis Trials

Adverse Event	Placebo	Celecoxib 50 mg BID	Celecoxib 100 mg BID	Celecoxib 200 mg QD	Celecoxib 200 mg BID	Celecoxib 400 mg BID	NSAID
No. Treated	1864	690	1779	453	1914	615	2098
Any event	6.1	7.5	7.4	3.3	7.8	6.8	9.7
Abdominal pain	0.6	0.9	0.7	0.2	0.9	0.3	2.1
Dyspepsia	0.6	0.4	0.8	0.0	0.9	0.8	1.6
Rash	0.6	1.2	0.8	0.4	0.9	1.1	0.3
Diarrhea	0.3	0.7	0.4	0.2	0.3	0.3	0.4
Nausea	0.6	0.3	0.6	0.4	0.4	0.3	0.9
Pruritus	0.2	0.0	0.4	0.0	<0.1	0.5	0.0
Esophageal ulceration	0.0	0.0	0.0	0.0	0.2	0.0	0.6

All numbers are percentages of patients unless otherwise specified.

Statistically significant differences for four types of adverse event causing withdrawal at an incidence ≥0.5% were evident between celecoxib and NSAIDs (Table 65). For rash and pruritus the incidences were higher for celecoxib; for abdominal pain and esophageal ulceration the difference represented higher incidences for NSAIDs. No statistically significant differences were apparent between celecoxib and placebo.

Table 65. Analysis of Adverse Events Causing Withdrawal between Celecoxib and Placebo or NSAIDs

Adverse Event	Celecoxib*	Placebo	p Value	Celecoxib*	NSAID	p Value
No. treated	3512	1864	-	2890	2098	-
Any event	7.3	6.1	-	8.5	9.7	-
Abdominal pain	0.7	0.6	-	0.9	2.1	<0.001
Dyspepsia	0.9	0.6	-	1.1	1.6	-
Rash	0.9	0.6	-	0.9	0.3	0.004
Diarrhea	0.4	0.3	-	0.3	0.4	-
Nausea	0.5	0.6	-	0.4	0.9	-
Pruritus	0.2	0.2	-	0.2	0.0	0.043
Esophageal ulceration	0.0	0.0	-	0.1	0.6	0.003

Data are expressed in percentages of patients (except for p values).
*Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

6.3.6.2 International Arthritis Trials

Table 66 shows the most common adverse events causing withdrawal in the International Arthritis Trials. Overall, the incidences of adverse events causing withdrawal were similar to those in the North American Controlled Arthritis Trials. The incidence for celecoxib 200 mg BID was higher than for 100 mg BID, due to the longer duration of the RA trial. Nine events led to withdrawal in at least 0.5% of patients in any treatment

group. For most of these events, the incidence was higher for diclofenac-treated patients than for the corresponding celecoxib group.

Table 66. Adverse Events Causing Withdrawal with Incidence ≥0.5% in Any Treatment Group: International Arthritis Trials

	6 Week OA (Study 042)		24 Week RA (Study 041)	
Adverse Event	**Celecoxib 100 mg BID**	**Diclofenac 50 mg BID**	**Celecoxib 200 mg BID**	**Diclofenac SR 75 mg BID**
No. treated	346	341	326	329
Any event	6.4	8.5	10.1	19.4
Abdominal pain	1.2	2.6	2.8	8.8
Diarrhea	0.6	1.5	1.8	3.0
Nausea	0.6	1.8	1.5	3.3
Rash	1.2	0.0	0.9	0.3
Dyspepsia	0.3	0.3	0.6	4.6
Vomiting	0.3	0.3	0.6	1.2
Dizziness	0.0	0.0	0.3	1.5
Rash erythematous	1.2	0.0	0.3	0.0
Flatulence	0.3	0.0	0.0	1.2

All numbers are percentages of patients unless otherwise specified.

The overall incidence of adverse events causing withdrawal was statistically significantly higher for diclofenac, and all three of the statistically significant differences in individual events (abdominal pain, nausea, and dyspepsia) represented higher incidences among diclofenac-treated patients than among those who received celecoxib.

6.3.6.3 North American Long-term Open Label Arthritis Study

A total of 6.6% of the patients discontinued Study 024 due to an adverse event. Fifty percent of these withdrawals took place during the first 90-day interval following initiation of treatment. The most common adverse events leading to withdrawal were abdominal pain (0.6%), rash (0.5%), dyspepsia (0.5%), diarrhea (0.4%), nausea (0.3%), and dizziness (0.3%).

6.3.7 Serious Adverse Events

None of the serious adverse events that occurred in patients receiving celecoxib were considered by a panel of external safety consultants to be related to study medication. Serious adverse events were defined as:

- fatal,
- life-threatening,

- permanently disabling,
- requiring, or prolonging, inpatient hospitalization,
- a congenital anomaly,
- a cancer, or
- an overdose.

6.3.7.1 Controlled Arthritis Trials

Table 67 shows the overall incidences of serious adverse events that occurred in all of the controlled arthritis trials combined, summarized by treatment group. The incidence of serious adverse events across all celecoxib dose groups were similar and generally lower than that observed for either placebo or the NSAID treatment groups. The highest incidence of serious adverse events related to gastrointestinal or myocardial function. There were 26 patients with serious gastrointestinal adverse events; 10 were NSAID-treated patients (1.9 events per 100 patient-years), five were placebo-treated patients (2.4 events per 100 patient-years), five were patients receiving 200 mg BID celecoxib treatment groups (1.1 events per 100 patient-years) and three were patients receiving 100 mg BID celecoxib (1.0 events per 100 patient-years). The remaining three serious gastrointestinal adverse events occurred in patients receiving either 25-40 mg BID celecoxib or 50 mg BID celecoxib.

Table 67. Overall Incidences of Serious Adverse Events by Dose Regimen: Controlled Arthritis Trials

	Placebo (N=1864)	Celecoxib						NSAID Control (N=2768)
		25-40 mg BID (N=253)	50 mg BID (N=690)	100 mg BID (N=2125)	200 mg QD (N=453)	200 mg BID (N=2240)	400 mg BID (N=615)	
Patients with any serious adverse event	30	1	5	26	2	49	7	59
Patient-years of exposure	207.5	15.0	116.1	289.3	47.1	465.7	87.1	535.0
Serious adverse events per 100 patient-years	14.5	6.7	4.3	9.0	4.2	10.5	8.0	11.0

There were 28 patients with serious myocardial adverse events including 13 patients with myocardial infarction and nine patients with angina pectoris. Serious myocardial adverse events occurred in 10 patients taking celecoxib 200 mg BID (2.1 events per 100 patient-years), seven placebo-treated patients (3.3 events per 100 patient-years), five patients receiving celecoxib 100 mg BID (1.7 events per 100 patient-years) and four

patients receiving NSAIDs (0.7 events per 100 patient-years). The remaining two serious myocardial adverse events occurred in patients receiving either celecoxib 200 mg QD or celecoxib 400 mg BID.

6.3.7.2 North American Long-term Open Label Arthritis Study

Table 68 summarizes the overall rates of serious adverse events occurring in the North American Long-term Open Label Arthritis Study by dose regimen. The incidence of serious adverse events in the North American Long-term Open Label Arthritis Study is similar to that observed in the controlled arthritis trials when normalized for duration of patient exposure. There were 26 patients with serious gastrointestinal adverse events in the long-term open-label arthritis trial yielding an incidence of 1.0 events per 100 patient-years as compared to 1.1 events per 100 patient-years for patients receiving 200 mg BID celecoxib in the controlled arthritis trials. There were 36 patients with serious myocardial adverse events in the North American Long-term Open Label arthritis trial resulting in an incidence of 1.3 events per 100 patient-years. This closely agrees with the incidence of serious myocardial adverse events observed with celecoxib in the controlled arthritis trials (1.7 events per 100 patient-years).

Table 68. Overall Incidences of Serious Adverse Events by Dose Regimen and Length of Exposure: North American Long-term Open-Label Arthritis Study

	100 mg BID	200 mg BID	300 mg BID	400 mg BID	Any Dose
Patients with any serious adverse event	56	114	35	42	244
Patient-years of exposure	518.8	1271.0	340.1	465.2	2672.4
Serious adverse events per 100 patient-years	10.8	9.0	10.3	9.0	9.1

6.3.7.3 Analgesia Trials

One serious adverse event occurred in the post-oral surgery studies: a rectal carcinoma discovered in a patient who received a single dose of celecoxib 100 mg in Study 005.

Nine serious adverse events occurred in the post-orthopedic or post-general surgery pain trials: four in placebo patients (back pain, dysphagia, abscess, and impaired healing); one in a patient receiving celecoxib 100 mg (pneumothorax); two in patients receiving celecoxib 200 mg (ileus and infection); and two in patients receiving Darvocet-N 50 (cellulitis and infection).

6.3.8 Deaths

There were 26 deaths in patients who participated in the North American Controlled Arthritis Trials or the North American Long-term Open Label Arthritis Study of celecoxib and nine additional deaths in patients participating in other ongoing studies, for an overall total of 35 deaths. None were considered by an external panel of safety consultants to have been related to study medication.

6.3.8.1 Deaths in Completed Controlled Trials and the North American Long-term Open Label Arthritis Study

There were eight deaths during the controlled trials or within 28 days after the last dose of study medication. Of these, four patients had received celecoxib (200 mg QD, 100 mg BID or 200 mg BID) and four patients received NSAIDs. Five deaths were due to cardiovascular causes. Two of the cardiovascular-related deaths occurrred in celecoxib-treated patients (2.0 cardiovascular deaths per 1000 patient-years) and three in patients receiving NSAIDs (5.6 cardiovascular deaths per 1000 patient-years).

Eighteen deaths occurred during the North American Long-term Open Label Arthritis Study or within 28 days after the last dose of study medication through May 1, 1998. Seven deaths occurred in patients who received 200 mg BID, two deaths in patients who received 300 mg BID and nine deaths in patients treated with celecoxib 400 mg BID. Fourteen deaths were related to cardiovascular causes yielding an incidence of 3.3 cardiovascular deaths per 1000 patient-years.

6.3.8.2 Deaths in Ongoing Studies

Nine deaths occurred in celecoxib studies that are ongoing. One death was in a post-surgical pain study (Study 082), one was in an open-label arthritis study (Study 058) (Investigational New Drug Application [IND] 48,395). Six deaths occurred in studies of Alzheimer's disease (IND 53,125), and one was in a chemoprevention study (IND 51,926 held by the NCI).

6.3.9 Clinical Laboratory Results

The studies used for this analysis are a subset of the 12-week North American Arthritis Trials that were used in the preceding analysis of adverse events. For analyses of all clinical laboratory results, the five pivotal 12-week arthritis trials that contained both a

placebo and active (naproxen) control group (Studies 020, 021, 022, 023, and 054) are used to facilitate a comparison of celecoxib versus placebo, celecoxib versus naproxen and naproxen versus placebo within the same group of studies. Mean changes in hematology and biochemistry and urinalysis laboratory results from baseline to the final treatment visit are shown for placebo, celecoxib and naproxen treatment groups in Tables 69-71. Due to the large total number of patients that were enrolled in these studies, many small changes in clinical laboratory values between treatment groups were statistically significant but not clinically meaningful. The incidence of clinically significant changes in laboratory results are discussed in the review of safety related to body systems. (Section 6.3.10).

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Table 69. Mean Changes in Hematology Laboratory Results: North American 12-Week Placebo- and Active-Controlled Arthritis Trials

Assessment (units)	Treatment	Number of Patients	Baseline Mean	Final Visit - Mean Change from Baseline
Hemoglobin (g/dL)	Celecoxib(a)	2183	13.64	0.00 * #
	Placebo	1075	13.69	0.06)
	Naproxen	1069	13.67	-0.18 *
Hematocrit	Celecoxib(a)	2183	0.414	0.002 #
	Placebo	1075	0.416	0.003
	Naproxen	1069	0.416	-0.003 *
RBC ($x10^{12}$/L)	Celecoxib(a)	2183	4.52	0.01 * #
	Placebo	1075	4.53	0.03
	Naproxen	1069	4.55	-0.05 *
WBC ($x10^9$/L)	Celecoxib(a)	2183	7.136	-0.201 * #
	Placebo	1075	7.075	0.017
	Naproxen	1069	7.053	0.047
Platelet Count ($x10^9$/L)	Celecoxib(a)	2171	271.8	-6.1 * #
	Placebo	1071	268.6	3.2
	Naproxen	1059	263.2	2.5
Neutrophil Count ($x10^9$/L)	Celecoxib(a)	2182	4.665	-0.142 * #
	Placebo	1073	4.543	0.053
	Naproxen	1067	4.564	0.044
Lymphocyte Count ($x10^9$/L)	Celecoxib(a)	2182	1.826	-0.04 *
	Placebo	1073	1.874	-0.010
	Naproxen	1067	1.852	-0.023
Monocyte Count ($x10^9$/L)	Celecoxib(a)	2182	0.454	-0.014 #
	Placebo	1073	0.461	-0.010
	Naproxen	1067	0.450	0.002
Eosinophil Count ($x10^9$/L)	Celecoxib(a)	2182	0.138	0.001 * #
	Placebo	1073	0.144	-0.014
	Naproxen	1067	0.140	0.026 *
Basophil Count ($x10^9$/L)	Celecoxib(a)	2182	0.053	-0.003 #
	Placebo	1073	0.054	-0.002
	Naproxen	1067	0.052	0.000
Partial Thromboplastin Time (sec.)	Celecoxib(a)	2028	27.95	0.12
	Placebo	996	27.86	0.44
	Naproxen	992	27.96	-0.19 *
Prothrombin Time (sec.)	Celecoxib(a)	2042	12.70	-0.02
	Placebo	1004	12.69	0.07
	Naproxen	1000	12.69	0.08

* Significantly different from placebo in change from Baseline; $p \leq 0.05$.
# Significantly different from naproxen in change from Baseline; $p \leq 0.05$.
a) Combines celecoxib 100 mg and 200 mg BID

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Table 70. Mean Changes in Biochemistry Laboratory Results: North American 12-Week Placebo- and Active-Controlled Arthritis Trials

Assessment (units)	Treatment	Number of Patients	Baseline Mean	Final Visit - Mean Change from Baseline
Total Bilirubin (μmol//L)	Celecoxib(a)	2189	8.4	0.2 #
	Placebo	1080	8.3	0.1
	Naproxen	1072	8.2	-0.1 *
Alkaline Phosphatase (U/L)	Celecoxib(a)	2185	70.1	0.5 * #
	Placebo	1079	69.9	1.8
	Naproxen	1071	70.8	-0.4 *
AST (U/L)	Celecoxib(a)	2189	21.5	-0.2
	Placebo	1080	21.4	-0.3
	Naproxen	1972	21.5	-0.4
ALT (U/L)	Celecoxib(a)	2189	20.4	-0.7 #
	Placebo	1080	20.2	-0.3
	Naproxen	1072	20.7	-1.3 *
CPK (U/L)	Celecoxib(a)	2189	104.1	-3.9 #
	Placebo	1080	99.7	-7.2
	Naproxen	1072	102.6	3.5 *
Creatinine (μmol//L)	Celecoxib(a)	2190	69.0	-2.1 #
	Placebo	1080	70.0	-1.4
	Naproxen	1072	69.9	-0.8
BUN (mmol/L)	Celecoxib(a)	2190	5.67	0.09 * #
	Placebo	1080	5.71	-0.48
	Naproxen	1072	5.70	0.51 *
Uric Acid (μmol//L)	Celecoxib(a)	2190	300.3	4.0 *
	Placebo	1080	299.5	9.1
	Naproxen	1072	302.8	2.1 *
Glucose (mmol/L)	Celecoxib(a)	2188	5.735	0.239
	Placebo	1080	5.659	0.331
	Naproxen	1071	5.779	0.126 *
Protein (g/L)	Celecoxib(a)	2190	71.5	-0.9 * #
	Placebo	1080	71.3	0.0
	Naproxen	1072	71.2	-1.3 *
Albumin (g/L)	Celecoxib(a)	2189	39.9	-0.7 #
	Placebo	1080	39.8	-0.6
	Naproxen	1072	39.6	0.2 *
Sodium (mmol/L)	Celecoxib(a)	2189	139.6	0.5
	Placebo	1078	139.6	0.3
	Naproxen	1071	139.6	0.3
Potassium (mmol/L)	Celecoxib(a)	2183	4.24	0.00 *
	Placebo	1075	4.22	-0.04
	Naproxen	1069	4.23	0.01 *
Chloride (mmol/L)	Celecoxib(a)	2189	105.0	0.1 *
	Placebo	1078	105.1	-0.3
	Naproxen	1071	105.0	0.1 *
Calcium (mmol/L)	Celecoxib(a)	2190	2.308	-0.025 *
	Placebo	1080	2.299	-0.004
	Naproxen	1072	2.300	-0.020 *
Inorganic Phosphorous (mmol/L)	Celecoxib(a)	2184	1.133	0.000 #
	Placebo	1079	1.136	-0.001
	Naproxen	1070	1.124	-0.043 *

* Significantly different from placebo in change from Baseline; $p \leq 0.05$.
# Significantly different from naproxen in change from Baseline; $p \leq 0.05$.
a) Combines celecoxib 100 mg and 200 mg BID

Table 71. Mean Changes in Urinalysis Laboratory Results: North American 12-Week Placebo- and Active-Controlled Arthritis Trials

Assessment (units)	Treatment	Number of Patients	Baseline Mean	Final Visit Mean Change from Baseline
Specific Gravity	Celecoxib(a)	2136	1.0183	0.0003 * #
	Placebo	1034	1.0186	-0.0007
	Naproxen	1040	1.0178	0.0012 *
pH	Celecoxib(a)	2136	5.4	-0.0 #
	Placebo	1034	5.4	-0.0
	Naproxen	1040	5.3	0.1 *
Urine RBC (/HPF)	Celecoxib(a)	2136	1.8	-0.2
	Placebo	1034	2.1	-0.5
	Naproxen	1040	1.5	0.2
Urine WBC (/HPF)	Celecoxib(a)	2136	2.7	-0.1
	Placebo	1034	2.8	0.3
	Naproxen	1040	2.4	0.1

* Significantly different from placebo in change from Baseline; $p \leq 0.05$.
# Significantly different from naproxen in change from Baseline; $p \leq 0.05$.
a) Combines celecoxib 100 mg and 200 mg BID

6.3.10 Grouped Safety Results

6.3.10.1 GI Effects

6.3.10.1.1 Adverse Events

Table 71 presents all GI adverse events with an incidence of 0.5% or more in any treatment group in the North American Controlled Arthritis Trials. The highest incidence of GI adverse events occurred in patients receiving NSAIDs and the incidences of individual GI adverse events were generally higher for patients receiving NSAIDs than for celecoxib for almost all doses. Little variation was evident among celecoxib doses and no increase in incidence with increasing doses was suggested.

Table 72. GI Adverse Events with Incidence ≥0.5% in Any Treatment Group: North American Controlled Arthritis Trials

		Celecoxib					
Adverse Event	**Placebo**	**50 mg BID**	**100 mg BID**	**200 mg QD**	**200 mg BID**	**400 mg BID**	**NSAID**
No. treated	1864	690	1779	453	1914	615	2098
Any GI event	18.5	24.1	23.8	15.5	27.8	23.3	35.4
Dyspepsia	6.2	8.1	8.7	4.6	9.9	8.1	12.0
Diarrhea	3.8	5.4	5.0	3.5	6.6	6.5	6.1
Abdominal pain	2.8	4.5	3.4	2.0	5.2	3.3	8.2
Nausea	4.2	3.8	3.6	2.4	3.7	3.6	5.6
Flatulence	1.0	2.3	2.1	2.2	2.3	2.0	3.7
Constipation	1.9	1.4	1.8	1.1	1.9	0.8	4.1
Tooth disorder	1.5	1.3	1.9	1.5	1.6	1.5	2.2
Vomiting	0.5	1.0	0.9	0.2	1.4	2.3	1.6
Hiatal hernia	<0.1	0.1	0.1	0.0	1.1	0.0	1.4
Gastroesophageal reflux	0.4	1.0	0.7	0.0	0.9	0.5	0.7
Gastroenteritis	0.7	1.2	0.8	0.4	0.8	0.8	1.0
Stomatitis	0.5	0.4	1.2	0.4	0.5	0.3	1.3
Esophageal ulceration	0.0	0.0	0.0	0.0	0.2	0.0	0.7
Gastric ulcer(a)	0.0	0.0	<0.0	0.0	0.1	0.0	0.5

All numbers are percentages of patients unless otherwise specified.

a) Symptomatic ulcers diagnosed by endoscopy or other means; ulcers found at scheduled visits in the UGI endoscopy studies were not recorded as adverse events.

Table 73 shows statistical analyses of the GI adverse events among treatment groups. In all eight GI adverse events for which the difference between celecoxib and NSAID was statistically significant, the incidence was higher for the NSAID. The incidence of dyspepsia, diarrhea and flatulence were significantly higher in celecoxib-treated patients when compared to placebo.

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Table 73. Analysis of GI Adverse Events between Celecoxib and Placebo or NSAID: North American Controlled Arthritis Trials

Adverse Event	Celecoxib*	Placebo	p Value	Celecoxib*	NSAID	p Value
No. treated	3512	1864	-	2890	2098	-
Any GI event	23.5	18.5	<0.001	27.7	35.4	<0.001
Dyspepsia	8.4	6.2	0.004	9.9	12.0	0.021
Diarrhea	5.4	3.8	0.008	6.2	6.1	-
Abdominal pain	3.5	2.8	-	4.9	8.2	<0.001
Nausea	3.6	4.2	-	3.8	5.6	0.002
Flatulence	2.1	1.0	0.003	2.2	3.7	0.003
Constipation	1.8	1.9	-	1.9	4.1	<0.001
Tooth disorder	1.7	1.5	-	1.9	2.2	-
Vomiting	0.9	0.5	-	1.3	1.6	-
Hiatal hernia	<0.1	<0.1	-	0.8	1.4	0.024
GE Reflux	0.6	0.4	-	0.9	0.7	-
Gastroenteritis	0/7	0.7	-	0.9	1.0	-
Stomatitis	0.9	0.5	-	0.8	1.3	-
Esophageal ulceration	0.0	0.0	-	0.1	0.7	0.002
Gastric ulcer	<0.1	0.0	-	0.1	0.5	0.020

Data are expressed in percentages of patients (except for p values).
* Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

The percentages of patients withdrawing due to a GI adverse event ranged from 0.7% to 3.2% in celecoxib groups, with no evidence of an escalation with increasing dose. This compares to withdrawal rates for GI adverse events of 6.3% NSAIDs and 2.0% for placebo. Only two individual GI adverse events led to withdrawal in more than 1.0% of patients in any treatment group: abdominal pain and dyspepsia. Both of these led to withdrawal more commonly in NSAID patients than in celecoxib patients. The difference between celecoxib and NSAIDs was statistically significant for abdominal pain (0.9% vs. 2.1%; p<0.001).

6.3.10.1.2 Summary and Conclusions

Celecoxib was superior to NSAIDs with respect to tolerability, as assessed by a lower incidence of GI adverse events, as well as withdrawals due to GI adverse events. Overall, GI adverse events with celecoxib were greater than placebo. However, the only GI adverse events that were frequent in occurrence (≥1%) and associated with significantly greater incidence or withdrawal rates for celecoxib than placebo included dyspepsia, flatulence, and diarrhea.

6.3.10.2 Hepatic Effects

6.3.10.2.1 Adverse Events

All hepatic adverse events reported by ≥0.5% of patients in any treatment group in the North American Controlled Arthritis Trials are listed in Table 74. Statistically significant differences between treatments are summarized in Table 75. The incidence of adverse events related to elevations in liver transaminases was significantly greater in patients treated with NSAIDs when compared to celecoxib-treated patients. No statistically significant differences were evident between celecoxib and placebo.

Table 74. Hepatic-Related Adverse Events as Reported by the Investigator with an Incidence ≥ 0.5%: North American Controlled Arthritis Studies

		Celecoxib					
Adverse Event	**Placebo (N=1864)**	**50 mg BID (N=690)**	**100 mg BID (N=1779)**	**200 mg QD (N=453)**	**200 mg BID (N=1914)**	**400 mg BID (N=615)**	**NSAID (N=2098)**
Any Hepatic Event	0.9	0.7	0.9	0.0	0.9	0.7	1.5
AST Elevated(a)	0.4	0.6	0.4	0.0	0..4	0.3	0.9
ALT Elevated(a)	0.5	0.4	0.6	0.0	0.5	0.3	1.0

Data are expressed as percent of patients.
a) Based on the Investigator's evaluation of clinical laboratory results and designation as an adverse event.

Table 75. Analysis of Hepatic Adverse Events Between Celecoxib and Placebo or NSAIDs

Adverse Event	**Celecoxib(a) (N=3612)**	**Placebo (N=1864)**	**p-value**	**Celecoxib(a) (N=2890)**	**NSAID (N=2098)**	**p-value**
Any Hepatic Event	0.8	0.9	-	0.8	1.5	0.026
AST Elevated(b)	0.4	0.4	-	0.3	0.9	0.008
ALT Elevated(b)	0.5	0.5	-	0.4	1.0	0.023

Data are expressed as percent of patients (except for p values).
a) Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.
b) Based on the Investigator's evaluation of clinical laboratory results and designation as an adverse event.

6.3.10.2.2 Adverse Events Causing Withdrawal

A total of 11 patients were withdrawn due to either a gall bladder disorder, abnormal hepatic function, or increased liver transaminases in the North American Controlled Arthritis Trials. There was one patient in the placebo group who withdrew (<0.1%), two each in the celecoxib 100 mg and 200 mg BID dose groups (0.1%), and 6 in the NSAID treatment group (0.3%). Analyses of these findings revealed no statistically significant results.

6.3.10.2.3 Serious Adverse Events

There were four serious adverse events related to the hepatic and biliary system in the controlled arthritis trials. Two of the patients who received NSAIDs developed a gall bladder disorder, one patient receiving placebo developed cholecystitis, and one patient taking celecoxib 100 mg BID developed cholecystitis. There were six serious adverse events in the Long-term Open Label Arthritis Study related to the hepatic and biliary system. All six were cases of cholelithiasis.

6.3.10.2.4 Clinical Laboratory Results

The incidence of clinical laboratory changes related to hepatic function that occurred in the North American 12-Week Placebo- and Active-controlled Arthritis Trials (Studies 020, 021, 022, 023 and 054) are summarized in Table 76. No significant treatment-related effects were observed. A low percentage of patients with normal Baseline clinical laboratory results were found to have changes for any liver function test in all three treatment groups.

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Table 76. Incidence of Liver Function Test Abnormalities : Placebo- and Active-Controlled 12-Week Arthritis Trials

Clinical Laboratory Parameter	Celecoxib 100 and 200 mg BID		Placebo		Naproxen 500 mg BID	
	No. of Patients(a)	%	No. of Patients(a)	%	No. of Patients(a)	%
Total Bilirubin	2181		1077		1069	
>26 µmol/L		0.4		0.4		0.1
>35 µmol/L		0.1		0.2		0
AST(b)	2188		1080		1072	
>75 U/L		0.1		0.2		0.2
>200 U/L		0		0.2		0.1
ALT(c)	2188		1080		1072	
>75 U/L		0.6		0.8		0.6
>200 U/L		0		0.1		0.1
Alk Phos(d)	2181		1079		1071	
>200 U/L		0.1		0		0
>500 U/L		0		0.1		0
Albumin	2180		1077		1068	
<30 g/L		0.8		0.6		0.1
<20 g/L		0		0		0

a) No. of patients with normal values at Baseline
b) AST; aspartate transaminase
c) ALT; alanine transaminase
d) Alk Phos; alkaline phosphatase

6.3.10.2.5 Hepatically Impaired Subjects: Study 016

The PK parameters, safety, and tolerability of a single dose of celecoxib 100 mg and after eight multiple doses of celecoxib 100 mg BID were examined in an open-label study of 23 patients with mild or moderate hepatic impairment based on the Child-Pugh Classification System.

There were no laboratory values for which the mean change from Baseline to Post-treatment was statistically significantly different for the mildly and moderately hepatically impaired subjects. When the mildly and moderately hepatically impaired subjects were analyzed separately, only mean total bilirubin levels decreased significantly from Baseline to Post-treatment within the group of mildly impaired subjects.

6.3.10.2.6 Summary and Conclusions

The results indicate that celecoxib is not associated with alterations in liver function or with adverse events due to liver or biliary tract disease. Celecoxib is metabolized in the

liver, and while clearance of celecoxib is reduced in the presence of moderate liver disease, the tolerability of the drug is not affected. Liver function test abnormalities were rare, and seen only at rates similar to or less than placebo and significantly less than NSAIDs.

6.3.10.3 Renal Effects

6.3.10.3.1 Adverse Events

The incidence of adverse events related to renal function that occurred at an incidence 0.5% or greater in patients who were enrolled into the North American Controlled Arthritis Trials are summarized in Table 77. Peripheral edema and hypertension were the most frequently reported adverse events.

Table 77. Renal Adverse Events as Reported by the Investigator with an Incidence ≥0.5% in Any Treatment Group: North American Controlled Arthritis Trials

Adverse Event	Placebo	Celecoxib					NSAID
		50 mg BID	100 mg BID	200 mg QD	200 mg BID	400 mg BID	
No. treated	1864	690	1779	453	1914	615	2098
Any renal event	2.5	3.6	2.9	4.4	5.6	5.5	4.1
Generalized edema	0.0	0.1	0.1	0.2	0.1	0.3	0.5
Peripheral edema	1.1	2.2	1.5	2.9	2.6	2.4	2.1
Hypertension	0.3	0.3	0.6	0.2	1.0	0.5	0.7
Aggravated hypertension	0.4	0.0	0.4	0.9	0.6	0.7	0.3

* All numbers are percentages of patients unless otherwise specified.

The incidence of peripheral edema associated with celecoxib was not dose related. Generalized edema was more often observed with the NSAIDs when compared to placebo or celecoxib. The incidence of hypertension or aggravated hypertension with celecoxib was similar to placebo and NSAIDs and no relationship to the administered dose of celecoxib was evident.

A comparison of statistically significant differences in the incidence of renal adverse events with the recommended therapeutic doses of celecoxib and either placebo or NSAIDs is presented in Table 78. The incidence of peripheral edema with celecoxib was significantly greater than placebo. The incidence of peripheral edema with the celecoxib

was comparable to NSAIDs, however; the incidence of generalized edema with celecoxib was significantly less than NSAIDs and comparable to placebo treatment.

Table 78. Analysis of Renal Adverse Events between Celecoxib and Placebo or NSAIDs

Adverse Event	Celecoxib*	Placebo	p Value	Celecoxib*	NSAIDs	p Value
No. treated	3512	1864	-	2890	2098	-
Any renal event	5.6	3.6	0.002	6.1	4.8	-
Generalized edema	0.1	0.0	-	0.1	0.5	0.031
Peripheral edema	2.1	1.1	0.007	2.3	2.1	-
Hypertension	0.6	0.3	-	0.8	0.7	-
Aggravated hypertension	0.6	0.4	-	0.6	0.3	-

Data are expressed in percentages of patients (except for p values).
*Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

An analysis of weight gain and blood pressure changes for patients with peripheral edema who were studied in the North American 12-Week Placebo- and Active-Controlled Arthritis Trials is shown in Table 79. The higher incidence of peripheral edema in celecoxib patients when compared to placebo patients was not associated with a corresponding significant change in mean body weight or blood pressure. Additionally, the incidence of patients with peripheral edema who gained one kilogram or more in body weight was similar across the treatment groups.